

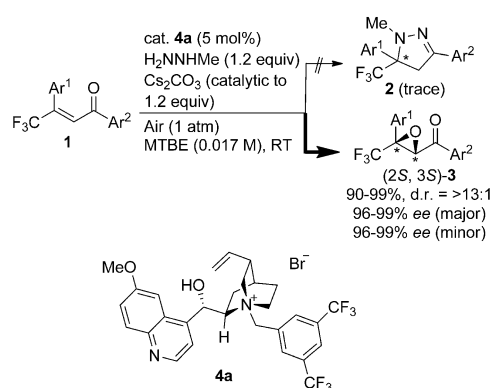
Synthetic Methodology

Enantioselective Synthesis of Epoxides Having a Tetrasubstituted Trifluoromethylated Carbon Center: Methylhydrazine-Induced Aerobic Epoxidation of β,β -Disubstituted Enones**

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Ever since the milestone of asymmetric epoxidation of allylic alcohols in the early 1980s by Katsuki and Sharpless,^[1] the catalytic asymmetric epoxidation of olefins has become one of the most powerful, well-explored, and reliable transformations in organic synthesis for providing enantiomerically enriched epoxides, which are versatile building blocks for the synthesis of biologically active molecules and advanced materials.^[2] A large number of catalytic systems for asymmetric epoxidation have been devised over three decades and can be categorized into three classes according to the combination of catalysts and oxidants: a) metal complex/active oxidant,^[1,3] b) metal complex/molecular oxygen,^[4] and c) organocatalyst/active oxidant.^[5] Despite tremendous efforts by many groups, the catalytic asymmetric epoxidation of acyclic β,β -disubstituted enones is still a challenge,^[6] particularly for β,β -disubstituted enones bearing a trifluoromethyl group at the β -position. In 2011, Yamamoto and co-workers provided a very nice solution to the catalytic asymmetric epoxidation of acyclic β,β -disubstituted enones with an iron complex consisting of $\text{Fe}(\text{OTf})_2$ and a carefully designed phenanthroline ligand.^[6b] This chiral iron phenanthroline system is effective for the asymmetric epoxidation of a variety of acyclic β,β -disubstituted enones, however, no example was shown for the asymmetric epoxidation of β,β -disubstituted enones having a β -trifluoromethyl group. In 2012, Feng and co-workers investigated chiral N,N' -dioxide-metal complexes for the epoxidation of β -monosubstituted enones including a β -trifluoromethyl group using hydrogen peroxide and found that optically active epoxides could be

obtained with excellent enantioselectivities, but method was not be applicable for β,β -disubstituted enones.^[7] We disclose herein the first asymmetric epoxidation of β,β -disubstituted enones **1**, having a β -trifluoromethyl group, by the serendipitous discovery of an aerobic organocatalytic system consisting of methylhydrazine (H_2NNHMe), a base, and a cinchona alkaloid phase-transfer catalyst (Scheme 1). Enantiomerically enriched trifluoromethylated epoxides with a tetrasubstituted carbon centers (**3**) were obtained for the first time, instead of the pyrazolines **2**, in excellent yields, excellent diastereoselectivities, and enantioselectivities (96–99% *ee*).



Scheme 1. Asymmetric aerobic epoxidation of β -trifluoromethyl- β,β -disubstituted enones **1** by a methylhydrazine/base/cinchona alkaloid system. MTBE = methyl *tert*-butyl ether.

Trifluoromethylated organic chemicals are finding increased utility in various fields including medicinal, biological, agricultural, and material chemistry. The trifluoromethyl group has a bigger van der Waals radius than a methyl group, the same electronegativity as oxygen an atom, and high lipophilicity, which often alters the physical, chemical, and physiological properties of the parent molecules when it is attached.^[8] Our group has been engaged in the development of the efficient synthesis of trifluoromethyl-containing organic molecules for more than a decade.^[9] During our recent research program directed at the catalytic asymmetric synthesis of biologically important isoxazolines, pyrrolines, and pyrazolines bearing a trifluoromethyl group at a chiral carbon center,^[10] we discovered an unprecedented asymmetric epoxidation of the β,β -disubstituted enones **3**, a reaction which could be a solution for a long-standing synthetic problem. Namely, when we attempted to synthesize trifluoro-

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methylated pyrazoline **2** by the treatment of (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-one (**1a**) with methylhydrazine (H_2NNHMe , 3.0 equiv) in the presence of the cinchona alkaloid **4a** (10 mol%) and Cs_2CO_3 (3.0 equiv) in $i\text{Pr}_2\text{O}$ (0.017 M) at ambient temperature, the enantioenriched epoxide (2*S*,3*S*)-**3a** with a trifluoromethylated quaternary carbon center was obtained, instead of **2**, in a 99% yield with excellent diastereoselectivity (>15:1) and excellent enantioselectivity of 98% *ee* (Table 1, entry 1). This exciting result

Table 1: Hydrazine-induced aerobic asymmetric epoxidation of **1a**: Optimization of reaction conditions.^[a]

Entry	Hydrazine	4	Base	Solvent	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c] Major	<i>ee</i> [%] ^[c] Minor
1	H_2NNHMe	4a	Cs_2CO_3	$i\text{Pr}_2\text{O}$	5	99	99	98
2	none	4a	Cs_2CO_3	$i\text{Pr}_2\text{O}$	24	NR	—	—
3	H_2NNHMe	4a	none	$i\text{Pr}_2\text{O}$	24	NR	—	—
4	H_2NNH_2	4a	Cs_2CO_3	$i\text{Pr}_2\text{O}$	20	5	n.d.	n.d.
5	H_2NNHPh	4a	Cs_2CO_3	$i\text{Pr}_2\text{O}$	20	7	n.d.	n.d.
6	H_2NNHAc	4a	Cs_2CO_3	$i\text{Pr}_2\text{O}$	20	7	n.d.	n.d.
7	H_2NNMe_2	4a	Cs_2CO_3	$i\text{Pr}_2\text{O}$	20	NR	—	—
8	H_2NNHMe	4a	Na_2CO_3	$i\text{Pr}_2\text{O}$	20	trace	n.d.	n.d.
9	H_2NNHMe	4a	K_2CO_3	$i\text{Pr}_2\text{O}$	24	70	96	98
10	H_2NNHMe	4a	KOH	$i\text{Pr}_2\text{O}$	3	93	97	97
11	H_2NNHMe	4a	KOAc	$i\text{Pr}_2\text{O}$	20	trace	n.d.	n.d.
12	H_2NNHMe	4a	$t\text{BuOK}$	$i\text{Pr}_2\text{O}$	20	CP	n.d.	n.d.
13	H_2NNHMe	4a	Cs_2CO_3	Et_2O	20	95	97	98
14	H_2NNHMe	4a	Cs_2CO_3	THF	1	99	97	97
15	H_2NNHMe	4a	Cs_2CO_3	MTBE	2	97	98	99
16	H_2NNHMe	4a	Cs_2CO_3	toluene	3	96	96	97
17	H_2NNHMe	4a	Cs_2CO_3	CH_2Cl_2	24	96	87	91
18	H_2NNHMe	4b	Cs_2CO_3	$i\text{Pr}_2\text{O}$	7	89	88	92
19	H_2NNHMe	4c	Cs_2CO_3	$i\text{Pr}_2\text{O}$	4	90	96	98
20	H_2NNHMe	4d	Cs_2CO_3	$i\text{Pr}_2\text{O}$	16	94	—45	—26
21 ^[d]	H_2NNHMe	4a	Cs_2CO_3	MTBE	2	92	98	98
22 ^[e]	H_2NNHMe	4a	Cs_2CO_3	MTBE	5	99	96	96
23 ^[f]	H_2NNHMe	4a	Cs_2CO_3	MTBE	6	91	99	98
24 ^[g]	H_2NNHMe	4a	Cs_2CO_3	MTBE	21	81	98	99

[a] The reaction of **1a** with hydrazine (3.0 equiv) was carried out in the presence of **4** (10 mol%) and base (3.0 equiv) in solvent (0.017 M) under air atmosphere at room temperature, unless otherwise noted. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. [d] Used 5 mol% of **4a**. [e] Used 1 mol% of **4a**. [f] Used 1.2 equiv of H_2NNHMe and Cs_2CO_3 , 5 mol% of **4a**. [g] Used 1.2 equiv of H_2NNHMe , 0.3 equiv of Cs_2CO_3 , 5 mol% of **4a**. THF = tetrahydrofuran.

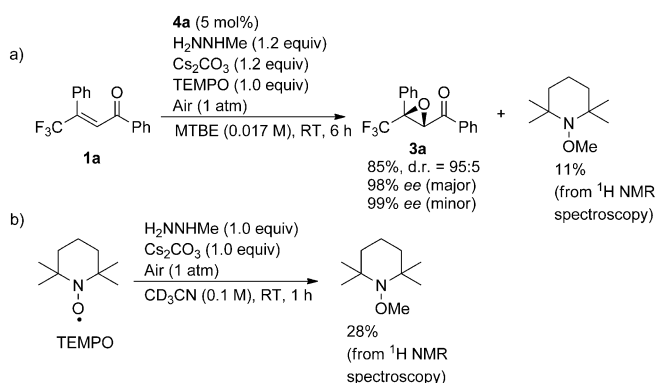
spurred us to investigate the detail of this unpredictable epoxidation reaction. No reaction took place in the absence of methylhydrazine (entry 2) or Cs_2CO_3 (entry 3). Low yields (5–7%) were obtained when other hydrazines such as H_2NNH_2 , H_2NNHPh , and H_2NNHAc were used instead of H_2NNHMe (entries 4–6). Moreover, no reaction occurred

when using dimethylhydrazine (H_2NNMe_2 ; entry 7). The choice of base was crucial to obtaining good reaction yields (entries 8–12), whereas the choice of solvent did not have significant effects (entries 13–17). This optimization resulted in the use of Cs_2CO_3 and MTBE as choice conditions with regard to both enantioselectivity and yield (entry 15). Other cinchona alkaloids (**4b**, **c**) were also effective for this transformation (entries 18 and 19) but the nature of the O protection had a clear influence only on the enantioselectivity (entry 20). The effect of the catalyst loading was further examined (entries 21–23). It should be noted that 1 mol% of **4a** gave a comparable result (96% *ee*; entry 22) to 5 mol% of **4a**. A catalyst loading of 5 mol% was chosen for the remaining experiments given the shorter reaction time and good enantioselectivity (entry 21). The amounts of H_2NNHMe and Cs_2CO_3 could be reduced to 1.2 equivalents without any sacrifice in yield of the isolated product, diastereo- and enantioselectivities (entry 23). Thus, the optimum reaction conditions required the use of 5 mol% of **4a**, 1.2 equivalents each of H_2NNHMe and Cs_2CO_3 in MTBE at ambient temperature under air. Interestingly, the catalytic amount of Cs_2CO_3 is enough for this transformation without any loss of the enantiomeric excess of **3a**, even though the chemical yield of **3a** is slightly lower (81% versus 91%) and a longer reaction time (21 h versus 6 h) is required under the catalytic conditions (entries 23 versus 24).

With optimal reaction conditions in hand (entry 23, Table 1), the scope of the H_2NNHMe -mediated aerobic asymmetric epoxidation of the β -trifluoromethyl-disubstituted enones **1** was explored (Table 2). A series of trifluoromethylated enone derivatives (**1a–f**, **h–n**) having a variety of substituents, such as methyl, methoxy, chloro, bromo and nitro groups, on the aromatic rings were nicely converted into the corresponding products **3a–f**, **h–n** in excellent yields with 96–99% *ee* (entries 3–7 and 9–15). The sterically demanding naphthyl-substituted enones **1g** and **1o** were also compatible with the same reaction conditions, thus affording products **3g** and **3o** in excellent yields with 99 and 98% *ee*, respectively (entries 8 and 16). The absolute stereochemistry of **3a** was clearly determined to be 2*S*,3*S* by X-ray analysis of the *O*-3,5-dichlorobenzoyl oxime derivative of **3a** (see Figure S1 in the Supporting Information), and all the other products were tentatively assigned by analogy with **3a**. The analogous ammonium bromide **4e** derived from quinine showed similar excellent enantioselectivity for **3a** with the opposite stereochemistry (2*R*,3*R*; 99%, 97% *ee*, entry 2).

Next we used ^{18}O -labeling experiments to elucidate the mechanism of this unprecedented epoxidation reaction. In particular, one task was to determine the origin of oxygen atom of the epoxide, that is, whether it came from molecular oxygen (air) or from water (moisture; Table 3). Epoxidation did not occur under an argon atmosphere without exposure to oxygen (entry 2), even in the presence of H_2^{18}O (entry 3). In contrast, the epoxidation of **1a** under an $^{18}\text{O}_2$ atmosphere quantitatively afforded the epoxide **3a** where ^{18}O incorporation into **3a** was 90% (entry 4). These results clearly indicate that the epoxide's oxygen atom originates from molecular oxygen in air, but not from trace amounts of water (i.e., moisture). Our next interest was the identification of an

radical **A** derived from H₂NNHMe, thus causing the first step of peroxide generation to be slow. Besides, H₂NNHMe should be oxidized easier than other hydrazine derivatives because of the electron-rich nitrogen atom. The reason why there was no reaction using H₂NNMe₂ (entry 7, Table 1) is that H₂NNMe₂ cannot furnish the radical intermediate **A** because of the lack of hydrogen on the corresponding nitrogen atom. The radical process was finally confirmed by the experiments using TEMPO for the scavenger of generated methyl radical (Scheme 3a). Moreover, to ascertain whether Cs₂CO₃ is truly capable of catalysis for oxidation of H₂NNHMe with oxygen, a process which is usually catalyzed by transition metals,^[11] the experiment as shown in Scheme 3b was carried out. Indeed, the formation of methylated TEMPO was observed.



Scheme 3. Experiments for the identification of methyl radical generated by the use of TEMPO.

In conclusion, we have discovered an unprecedented, asymmetric aerobic epoxidation induced by H₂NNHMe. The aerobic epoxidation of β -trifluoromethyl- β , β -disubstituted enones catalyzed by cinchona alkaloids under air in the presence of a base and H₂NNHMe provides enantiomerically enriched trifluoromethyl-substituted epoxides in excellent yields and enantioselectivities (96–99% ee). These epoxides can serve as potential building blocks in the field of medicinal, agrochemical, and material chemistry. The key for this success was the unique behavior of H₂NNHMe in the presence of oxygen with a base for the generation of pure hydrogen peroxide. Methylhydrazine is indispensable for aerobic epoxidation and this phenomenon would not have been discovered had used other hydrazine derivatives. Non-transition-metal activation of molecular oxygen is unique and, to the best of our knowledge, the aerobic system does not fall into the reported category of catalytic epoxidation. Further work on the application of this methylhydrazine-induced asymmetric aerobic epoxidation is in progress.^[15]

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- [12] We sincerely acknowledge one of the reviewers on our manuscript for his/her smart suggestion concerning mechanism of our oxidation system.
- [13] The base is indispensable for this oxidation since no reaction was observed in the absence of base (entry 3, Table 1).
- [14] Although a catalytic amount of base is enough for this oxidation (entry 24, Table 1), we used a stoichiometric amount of base because of the shorter reaction time and higher chemical yields. This could be explained by a poor solubility of base in organic solvent.
- [15] It should be noted that this hydrazine-induced aerobic epoxidation is not only applicable to trifluoromethyl-disubstituted enones, but also to nonfluorinated disubstituted enones, that is, aerobic epoxidation of the nonfluorinated analogue of **1a**, (*Z*)-1,3-diphenylbut-2-en-1-one, in the presence of **4a** (5 mol%), H₂NNHMe (3.0 equiv), and Cs₂CO₃ (3.0 equiv) in MTBE gave the nonfluorinated analogue of **3a**, ((2*S*,3*R*)-3-methyl-3-phenyl-oxiran-2-yl)(phenyl)methanone, in 71 % yield as a major isomer (d.r. = 73:27), though no enantioselectivity was observed (6% *ee*).